(+)-*cis*-8-Hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin: A Potent and Highly Stereoselective 5-Hydroxytryptamine Receptor Agonist

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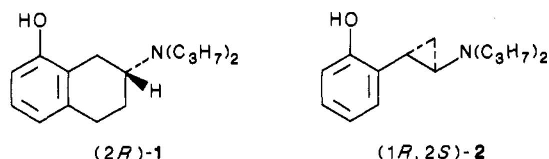
C1-Methylated derivatives of the potent 5-hydroxytryptamine (5-HT) receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT, 1) were synthesized and tested for central 5-HT and dopamine receptor activity by use of a biochemical test method in rats. *cis*-8-Hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin (8) was found to be a 5-HT receptor agonist. The (+)-enantiomer of 8 had a potency equal to that of 1, whereas (−)-8 and the trans isomer (±)-9 were inactive.

We have previously reported on two structurally different classes of novel 5-hydroxytryptamine (5-HT) receptor agonists, N-substituted 8-hydroxy-2-aminotetralins[1,2] and monophenolic N,N-dialkylated *trans*-2-phenylcyclopropylamines.[3] The similarities in the structure–activity relationships in the two classes of 5-HT agonists are striking. In both series, optimal 5-HT receptor agonist potency was conferred by *N,N*-di-*n*-propyl or *N*-ethyl substitution.[2,3] O-Methylation of the 5-HT active 8-hydroxy-2-aminotetralins[2] or of the 2- or 3-hydroxy derivatives of *trans*-2-phenylcyclopropylamine[3] results in a reduction in potency, similar in both series of compounds. Furthermore, the main structural features of the most prominent members of each series, 1 (8-OH DPAT) and 2, are similar; that is, the hydroxy group, the benzene ring, and the nitrogen atom of compound 2 can be brought to coincide with the corresponding structural elements of 1. However, 2 displays high stereoselectivity in the 5-HTP accumulation test,[3] while (+)-1 is only twice as potent as (−)-1.[1,2]

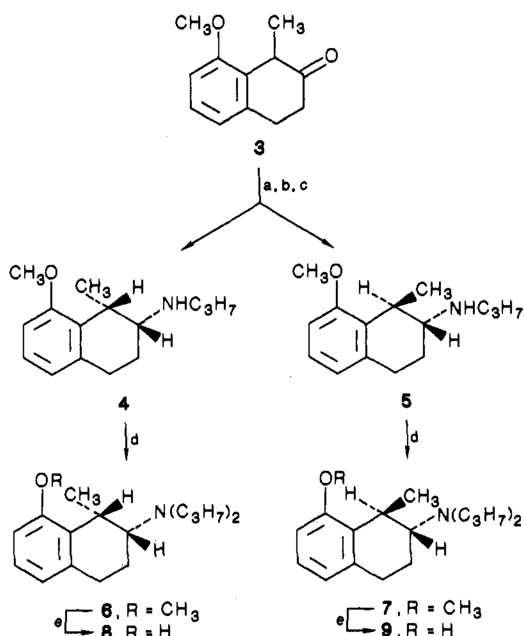


When 2 is superimposed on 1, as described above, the methylene group of the cyclopropyl ring of 2 assumes a relative spatial position that might correspond to that of a C1-methyl substituent in 1. Thus, in order to improve the stereoselectivity of the 8-hydroxy-2-aminotetralin derivatives and to further elucidate the structural features required for 5-HT receptor activation, we have now synthesized the C1-methylated derivatives of 1.

Chemistry

The syntheses of *cis*- and *trans*-8-methoxy-1-methyl-2-(di-*n*-propylamino)tetralin (6 and 7) are outlined in Scheme I. The reductive amination of 8-methoxy-1-methyl-2-tetralone (3)[4] proceeded with relatively poor stereocontrol (cis/trans ratio, 74:26). When the isomeric 5-methoxy-1-methyl-2-tetralone was subjected to reductive amination, by use of the same reaction conditions, only minor amounts of the trans isomer were obtained.[5] The pure cis (4) and trans isomers (5) were obtained after separation by flash chromatography[6] and recrystallization. N-Alkylation of 4 and 5 with 1-iodopropane afforded the

Scheme I[a]



[a] Reagents: a = n-$C_3H_7NH_2$, TsOH; b = H_2, Pd/C; c = flash chromatography and recrystallization; d = n-C_3H_7I, K_2CO_3; e = 47% HBr.

tertiary amines 6 and 7, which were converted into the phenols 8 and 9 by way of demethylation in 47% aqueous HBr. The relative stereochemistry of the cis (4) and the trans isomers (5) was established unambiguously by X-ray crystallography.[7]

In order to prepare the enantiomers of the 5-HT active 8, the racemic intermediate 4 was resolved into the enantiomers by fractional crystallization of diastereomeric salts. Two crystallizations of the di-*p*-toluoyl-D-tartrate of (±)-4 from methanol–water afforded (+)-4. The (−)-enantiomer

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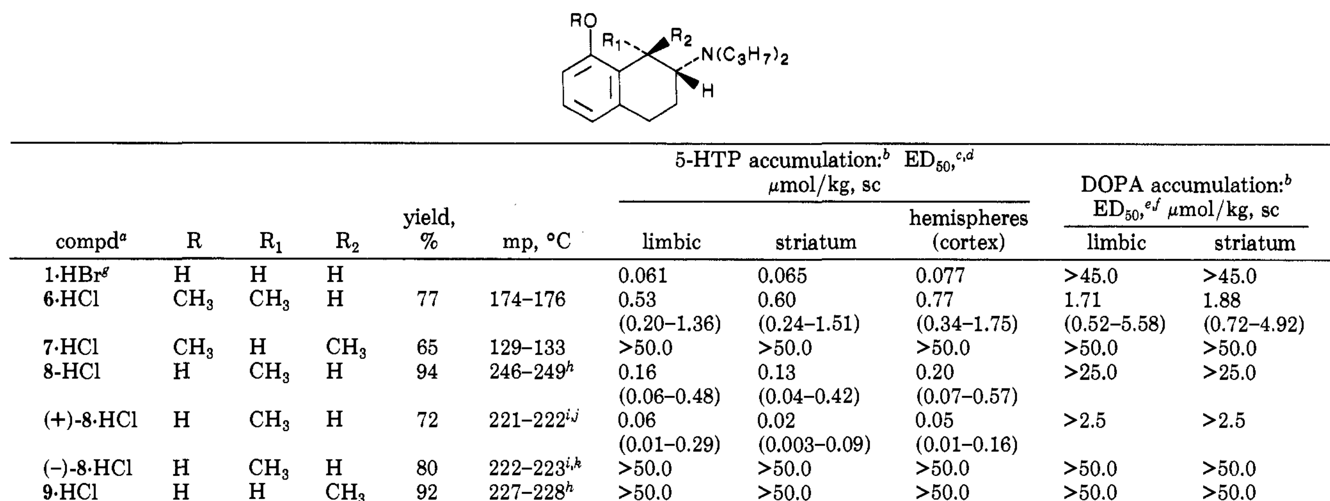
Table I. Effects of C1-Methylated 2-Aminotetralins on Rat Brain 5-HTP and DOPA Formation



compd[a]	R	R_1	R_2	yield, %	mp, °C	5-HTP accumulation:[b] ED_{50},[c,d] μmol/kg, sc: limbic	striatum	hemispheres (cortex)	DOPA accumulation:[b] ED_{50},[e,f] μmol/kg, sc: limbic	striatum
1·HBr[g]	H	H	H			0.061	0.065	0.077	>45.0	>45.0
6·HCl	CH_3	CH_3	H	77	174–176	0.53 (0.20–1.36)	0.60 (0.24–1.51)	0.77 (0.34–1.75)	1.71 (0.52–5.58)	1.88 (0.72–4.92)
7·HCl	CH_3	H	CH_3	65	129–133	>50.0	>50.0	>50.0	>50.0	>50.0
8·HCl	H	CH_3	H	94	246–249[h]	0.16 (0.06–0.48)	0.13 (0.04–0.42)	0.20 (0.07–0.57)	>25.0	>25.0
(+)-8·HCl	H	CH_3	H	72	221–222[i,j]	0.06 (0.01–0.29)	0.02 (0.003–0.09)	0.05 (0.01–0.16)	>2.5	>2.5
(−)-8·HCl	H	CH_3	H	80	222–223[i,k]	>50.0	>50.0	>50.0	>50.0	>50.0
9·HCl	H	H	CH_3	92	227–228[h]	>50.0	>50.0	>50.0	>50.0	>50.0

[a] Racemate unless otherwise denoted. [b] For experimental details, see the Experimental Section and ref 9. [c] Dose giving a half-maximal decrease of 5-HTP formation in the rat brain part, estimated from a dose–response curve comprising five to six dose levels (n = 3–4). The maximal reduction of the 5-HTP level was empirically found to be 50% from the control levels (209 ± 5 ng of 5-HTP/g of limbic tissue, 133 ± 5 ng of 5-HTP/g of striatal tissue, and 125 ± 6 ng of 5-HTP/g of hemispheral tissue (n = 26–30). [d] Shown in parentheses are the 95% confidence limits of the ED_{50} values. [e] Dose giving a half-maximal decrease of DOPA formation in the rat brain part, estimated from dose–response curve comprising three to five dose levels (n = 3). The maximal reduction of the DOPA level was empirically found to be 65% from control level (877 ± 30 ng of DOPA/g of tissue) for the limbic and 80% from the control level (2283 ± 76 ng of DOPA/g of tissue) for the striatal brain portions. [f] The ED_{50} values for decreasing DOPA formation in he hemispheral rat brain portion are greater than the highest doses tested: >50.0 μmol/kg for compounds (+)-1, 7, (−)-8, and 9; >25.0 μmol/kg for compounds 6 and 8; >2.5 μmol/kg for compound (+)-8. [g] Values are from ref 2. [h] From EtOH–ether. [i] From acetonitrile–ether. [j] $[\alpha]_D^{22}$ +40.9° (c 1.01, CH_3OH). [k] $[\alpha]_D^{22}$ −43.7° (c 1.02, CH_3OH).

of 4 was obtained from the recovered base of the mother liquors after two crystallizations of the di-*p*-toluoyl-L-tartrate. N-Alkylation of (+)-4 and (−)-4 with 1-iodopropane afforded the tertiary amines (+)-6 and (−)-6, respectively. Subsequent demethylation by use of 47% aqueous HBr furnished the desired phenols (+)-8 and (−)-8.

Pharmacology

The compounds were tested in reserpinized rats by using a previously described biochemical test method.[8] Behavioral observations were made throughout the experiments.

The in vivo biochemical test method utilizes the well-established phenomenon of receptor-mediated feedback inhibition of the presynaptic neuronal activity.[9] Thus, the rate of synthesis of 5-HT is inhibited by 5-HT agonists. Similarly, the synthesis of dopamine (DA) and norepinephrine (NE) is inhibited by agonists activating DA and NE receptors, respectively. The 5-HTP accumulation, following decarboxylase inhibition by means of (3-hydroxybenzyl)hydrazine (NSD 1015), was thus used as an indicator of the rate of synthesis of 5-HT in the three brain parts (limbic, striatum, and hemispheres). The DOPA accumulation was taken as an indicator of the rate of synthesis of DA in DA-predominated parts (i.e., limbic system, corpus striatum) and the rate of synthesis of NE in the NE-dominated remaining hemispheral portions (mainly cortex). The results obtained in the biochemical test are presented in Table I.

Results and Discussion

The rat brain 5-HT synthesis (5-HTP accumulation) was decreased by (±)-6, (±)-8, and (+)-8, whereas the DA synthesis (DOPA accumulation) was decreased only by (±)-6. The other compounds investigated, (±)-7, (−)-8, and (±)-9, were considered inactive in the biochemical test system employed.

The high stereoselectivity of the cis isomer 8 in the biochemical assay in noteworthy. Furthermore, the active enantiomer, (+)-8, seems to be approximately equipotent with the selective 5-HT receptor agonist 1 (8-OH DPAT).[10] In addition, both 1 and 8 have been shown to facilitate male rat sexual behavior, tentatively by stimulating 5-HT receptors.[11] In similar fashion to (±)-1 (10 μmol/kg, sc), (+)-8 (20 μmol/kg, sc) also induced marked forepaw extension and treading in reserpinized (5 mg/kg, ip) rats. However, other aspects of the 5-HT motor syndrome[12] (hindlimb abduction, flat body posture, and Straub tail reaction) were less pronounced after (+)-8 than after 1. This might indicate a slight difference in pre- versus postsynaptic 5-HT receptor selectivity profile between these compounds.

In contrast to 1, which is a more flexible molecule, the C1-methyl-substituted 8 preferentially adopts half-chair

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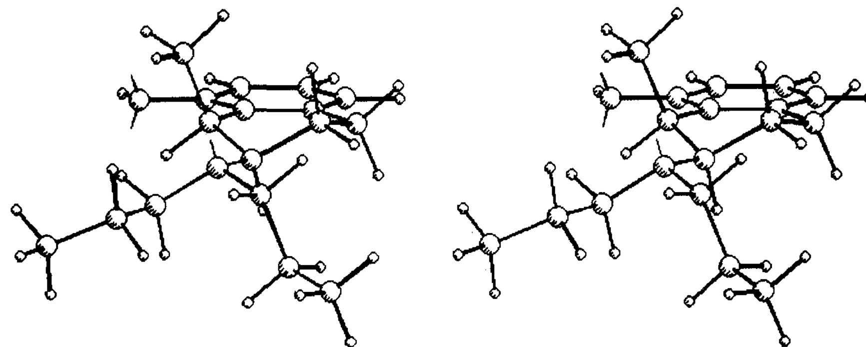

Figure 1. Computer-generated stereo pair of the lowest energy molecular mechanics (MMP2) conformation of (+)-8. For further details, see ref 7.

conformations in which the dipropylammonium substituent (which is pseudoequatorially oriented) adopts only one out of three possible staggered rotamers (this conclusion is supported by results from X-ray crystallography, ^{1}H and ^{13}C NMR experiments, and molecular mechanics calculations; the lowest energy MMP2 conformation of (+)-8 is depicted in Figure 1).[7,13] The high potency of (+)-8 and its restricted mobility makes it a key compound when discussing SAR of 5-HT receptor agonists. The drastic increase in stereoselectivity that was achieved by introducing a cis C1-methyl substituent in 1 may be due to the steric bulk of the pseudoaxial methyl group, which may prevent the inactive enantiomer [(−)-8] from interacting properly with the 5-HT receptors (for a thorough discussion, see ref 7). The inactivity of the racemic trans derivative (±)-**9**, on the other hand, appears to be related to its reluctance to adopt half-chair tetralin ring conformations with dipseudoequatorial substituents.[7]

Experimental Section

Chemistry. Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. ^{1}H NMR spectra were recorded on a JEOL FX 90 Q spectrometer and referenced to internal tetramethylsilane. Mass spectra,[14] recorded at 70 eV on a 9000 LKA spectrometer, were all in accordance with the assigned structures. Resolved and racemic compounds gave identical NMR and mass spectra. Optical rotations were obtained with a Perkin-Elmer 241 polarimeter. The elemental analyses (C, H and N) were performed by Mikro Kemi AB, Box 19025, S-750 19 Uppsala, Sweden. For purity tests, TLC was performed on fluorescent silica gel or alumina plates. Only one spot (visualized by UV light and I_2 vapor) was obtained for all compounds. GC was performed on a Varian 2700 instrument with a flame-ionization detector. A glass column (3 m) with 3% OV-17 on 80–100-mesh Varaport 30 was used. HPLC was performed on a Waters 5 Si 10 column with hexane–ethyl acetate–ethanol (82:15:3) as mobile phase, working in the pressure range 1000–3000 psi and with the flow rate 2 mL/min. Detection was made with a Waters Model 440 UV monitor.

8-Methoxy-1-methyl-2-tetralone (3).[4,15] Compound **3** was prepared by a procedure previously described by Taylor:[4] A mixture of 8-methoxy-2-tetralone[16] (50 g, 284 mmol), pyrrolidine (45 mL, 544 mmol), dry benzene (300 mL), and *p*-toluenesulfonic acid monohydrate (50 mg, 0.3 mmol) was heated to reflux in the presence of a Dean–Stark apparatus for 24 h. The volatiles were evaporated, and the residue was dissolved in dioxane (250 mL). Iodomethane (85 mL, 1.33 mol) was added, and the resulting solution was stirred at 40 °C for 3 h and then at 75 °C for 21 h. An additional portion of iodomethane (30 mL, 469 mmol) was added, and the heating was continued for 17 h. Water (110 mL) and acetic acid (5 mL) were added, and the mixture was heated to reflux for 5 h. The volatiles were evaporated, and the residue was partitioned between chloroform and aqueous 1 M hydrogen chloride. The organic layer was dried (magnesium sulfate) and concentrated. Distillation gave 54 g (82%) of pure **3**, bp 105-110 °C (0.20–0.25 mmHg) [lit.[4] bp 142 °C (1 mm Hg)].

***cis*-8-Methoxy-1-methyl-2-(*n*-propylamino)tetralin (4) and *trans*-8-Methoxy-1-methyl-2-(*n*-propylamino)tetralin (5).** A solution of **3** (15.0 g, 79 mmol), *n*-propylamine (13.5 mL, 164 mmol), and *p*-toluenesulfonic acid monohydrate (50 mg, 0.3 mmol) in 300 mL of dry benzene was heated to reflux under nitrogen in the presence of a Dean-Stark apparatus. After 48 h, the volatiles were evaporated in vacuo and the residue was dissolved in 150 mL of methanol. Palladium (10%) on carbon was added, and the hydrogenation was performed at atmospheric pressure. When the uptake of hydrogen was complete, the reaction mixture was filtered (Celite) and concentrated in vacuo. The residual oil was passed through a short alumina column with ether–petroleum (1:1) as eluant to afford an oil. The ratio of **4**/**5** was determined by GC to be 74:26 (230 °C; **4** t_R = 6.3 min; **5**, t_R = 5.0 min). The crude product was purified on a silica gel (Merck, particle size 40–63 μm) column (88 mm od.; 50-mL fractions) by use of flash chromatography.[6] The column was packed and eluted with ammonia saturated ether–light petroleum (4:1).[17] Fractions 500–750 mL gave, after precipitation with ethereal HCl, 2.1 g of **5**·HCl. Fractions 1100–2150 mL afforded 2.0 g of **4**·HCl. The combined intermediate fractions were treated with ethereal HCl, and the collected solid was recrystallized twice from acetonitrile-methanol to give 5.5 g of **4**·HCl. Additional portions of **5**·HCl (0.9 g) and **4**·HCl (0.5 g) were recovered from the combined mother liquors by flash chromatography. This procedure gave 8.0 g (38%) of **4**·HCl and 3.0 g (14%) of **5**·HCl. **4**·HCl: mp 243–245 °C; GC (230 °C) homogeneous; ^{1}H NMR (CD_3OD) δ 1.06 (t, 3 H), 1.14 (d, 3 H), 1.55–2.30 (m, 4 H), 2.80–3.90 (m, 6 H), 3.83 (s, 3 H), 6.60–6.90 (m, 2 H), 7.00–7.25 (m, 1 H); MS, *m/z* (relative intensity) 233 (65), 204 (82), 175 (100). Anal. ($C_{15}H_{23}NO{\cdot}HCl$) C, H, N. **5**·HCl: mp 175–176 °C; GC (230 °C) homogeneous; ^{1}H NMR (CD_3OD) δ 1.00 (t, 3 H), 1.29 (d, 3 H), 1.50–2.50 (m, 4 H), 2.70–3.15 (m, 4 H), 3.20–3.60 (m, 2 H), 3.84 (s, 3 H), 6.65–6.90 (m, 2 H), 7.00–7.25 (m, 1 H); MS, *m/z* (relative intensity) 233 (65), 204 (83), 175 (100). Anal. ($C_{15}h_{23}NO{\cdot}HCl$) C, H, N.

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(17) Prepared by shaking 5 mL of NH_4OH, 800 mL of ether, and 200 mL of petroleum. The decanted organic layer was used.

Resolution of *cis*-8-Methoxy-1-methyl-2-(*n*-propylamino)tetralin (4). A 4.76-g (17.6-mmol) sample of 4·HCl was converted into the free amine by basification with 10% aqueous sodium carbonate and extraction with ether. The ethereal solution of 4 was dried (potassium carbonate) and concentrated in vacuo. The free base of 4 and 8.47 g (20.9 mmol) of (+)-di-*p*-toluoyl-D-tartaric acid were dissolved in 50 mL of hot methanol. Water (8 mL) was added, and the solution was allowed to cool at room temperature overnight. Filtration gave 5.81 g of crystals [$[\alpha]^{22}_D$ +101° (*c* 1.07, CH_3OH)], which were recrystallized from methanol-water (25:4) to yield 4.89 g of diastereomeric salt [$[\alpha]^{22}_D$ +103° (*c* 1.06, CH_3OH)]. The amine was liberated by treatment with 1 M aqueous sodium hydroxide (200 mL) and extracted with ether (3 × 150 mL). The combined ether layers were dried (potassium carbonate), filtered, and concentrated in vacuo to give an opaque oil, which was passed through a short alumina column with ether as the eluant. Evaporation of volatiles gave 1.73 g (84%) of (+)-4. A small sample was treated with ethereal HCl to produce a jelly that was difficult to filter. Recrystallization from acetonitrile also gave a jelly. Filtration and drying afforded (+)-4·HCl: mp 215–217 °C; $[\alpha]^{22}_D$ +30.4° (*c* 1.02, CH_3OH). Anal. ($C_{15}H_{23}NO{\cdot}HCl$) H, N; C: calcd, 66.67; found, 66.2.

The combined mother liquors from above were concentrated, and the residue was treated with 1 M aqueous sodium hydroxide. The free amine was extracted with ether, and the combined ether layers were dried and concentrated in vacuo to afford 3.10 g of free base as an oil, which contained some ether. This oil and 5.37 g (13.3 mmol) of (–)-di-*p*-toluoyl-L-tartaric acid were dissolved in 50 mL of methanol, and 8 mL of water was added. The crystals that formed upon cooling were collected and recrystallized from methanol–water (25:4) to give 4.02 g of diastereomeric salt [$[\alpha]^{22}_D$ –105° (*c* 1.00, CH_3OH)]. The amine was liberated and treated as described above to afford 1.40 g (68%) of (–)-4. A small sample was converted to the HCl salt, which was recrystallized from acetonitrile to produce a jelly. Filtration and drying afforded (–)-4·HCl: mp 217–218 °C; $(\alpha)^{22}_D$ –31.1° (*c* 1.00, CH_3OH). Anal. ($C_{15}H_{23}NO{\cdot}HCl$) H, N; C: calcd, 66.77; found, 66.15.

Determination of the Enantiomeric Excess of (+)-4 and (–)-4. Compound (–)-4 (20 mg, 0.09 mmol) was mixed with 0.52 mL of water, 0.12 mL of 1 M aqueous sodium hydroxide, and 0.52 mL of dichloromethane. A 0.1 M solution of (*R*)-2-methoxy-2-phenylacetyl chloride (1.07 mL, prepared from (*R*)-2-methoxy-2-phenylacetic acid and thionyl chloride) in dichloromethane was added with vigorous stirring. After 1 h, 1 M aqueous sodium hydroxide (5 mL) and dichloromethane (5 mL) were added. The organic layer was washed with 1 M aqueous HCl, dried (magnesium sulfate), filtered, and concentrated in vacuo. The (*R*)-2-methoxy-2-phenylacetamide of (+)-4 was prepared by use of the same procedure. These amides were subjected to HPLC analysis. The enantiomeric excess (% ee) of (–)-4 and (+)-4 was estimated to be 98% ee and 97% ee, respectively, by comparison of the relative peak areas of the (*R*)-2-methoxy-2-phenylacetamides of (–)-4 (t_R = 2.5 min) and (+)-4 (t_R = 4.5 min).

***cis*-8-Methoxy-1-methyl-2-(di-*n*-propylamino)tetralin (6).** Compound 4·HCl (1.00 g, 3.7 mmol) was converted into the free amine by alkalinization (50 mL of 10% aqueous sodium carbonate), and extraction with ether (3 × 50 mL). The ether extracts were combined, dried, (potassium carbonate), and filtered. The filtrate was concentrated in vacuo, and the residual oil was dissolved in 20 mL of acetonitrile. 1-Iodopropane (0.41 mL, 4.1 mmol) and finely ground potassium carbonate (1.28 g, 9.3 mmol) were added, and the mixture was stirred at 25 °C. After 2 days, additional amounts (as above) of 1-iodopropane and potassium carbonate were added, and the reaction was allowed to continue for 2 days more at 50 °C. The volatiles were evaporated in vacuo, and the residue was partitioned between 10% aqueous sodium carbonate (50 mL) and ether (3 × 50 mL). The combined ether layers were dried (potassium carbonate), filtered, and concentrated in vacuo. The remaining oil was chromatographed on an alumina column eluted with ether–petroleum (1:4) and was then treated with ethereal HCl.

Recrystallization from acetonitrile–ether afforded 0.89 g (77%) of 6·HCl: mp 174–176 °C; GC (240 °C) homogeneous, t_R = 8.2 min; ^1H NMR (CD_3OD) δ 1.05 (t, 6 H), 1.26 (d, 3 H), 1.55–2.40 (m, 6 H), 2.85–3.90 (m, 8 H), 3.84 (s, 3 H), 6.60–6.90 (m, 2 H), 7.00–7.30 (m, 1 H); MS, *m/z* (relative intensity) 275 (16), 246 (96), 175 (100). Anal. ($C_{18}H_{29}NO{\cdot}HCl$) C, H, N.

(–)-*cis*-Methoxy-1-methyl-2-(di-*n*-propylamino)tetralin [(–)-6]. Compound (–)-4 (0.80 g) was converted to (–)-6 by the same method. Recrystallization from methanol-ether afforded 0.79 g (74%) of (–)-6·HCl: mp 145–146 °C; $[\alpha]^{22}_D$ –40.0° (*c* 1.00, CH_3OH). Anal. ($C_{18}H_{29}NO{\cdot}HCl$) H, N; C: calcd, 69.32; found, 68.9.

(+)-*cis*-8-Methoxy-1-methyl-2-(di-*n*-propylamino)tetralin [(+)-6]. Compound (+)-6 was prepared from (+)-4 (1.00 g) by the same method. Recrystallization from methanol–ether gave 1.01 g (76%) of (+)-6·HCl: mp 145–146 °C; $[\alpha]^{22}_D$ +38.1° (*c* 1.00, CH_3OH). Anal. ($C_{18}H_{29}NO{\cdot}HCl$) H, N; C: calcd, 69.32; found, 68.4.

***trans*-8-Methoxy-1-methyl-2-(di-*n*-propylamino)tetralin (7).** Compound 5·HCl (1.00 g) was converted to the free base, which was N-alkylated by the same method. Recrystallization from acetonitrile–ether afforded 0.75 g (65%) of 7·HCl: mp 129–133 °C; GC (240 °C) homogeneous, t_R = 4.9 min; ^1H NMR (CD_3OD) δ 0.96 (t, 6 H), 1.29 (d, 3 H), 1.50–3.90 (m, 14 H), 3.86 (s, 3 H), 6.60–6.95 (m, 2 H), 7.05–7.30 (m, 1 H); MS, *m/z* (relative intensity) 275 (20), 246 (100), 175 (91). Anal. ($C_{18}H_{29}NO{\cdot}HCl$) C, H, N.

Demethylation of Methoxy Compounds. The phenols were obtained by heating a stirred solution of the appropriate methoxy compound in 47% aqueous HBr for 2 h at 120 °C under nitrogen. The volatiles were evaporated in vacuo. The residue was treated with saturated aqueous sodium bicarbonate. Extraction with ether (three times), drying (sodium sulfate), filtration, and evaporation of volatiles gave the free base, which was precipitated from ether with ethereal HCl. Recrystallization solvents, yields, and melting points for the prepared compounds are given in Table I. Additional data for 8 and 9 are given below.

***cis*-8-Hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin (8):** GC (240 °C) homogeneous, t_R = 10.0 min; ^1H NMR (CD_3OD) δ 1.06 (t, 6 H), 1.29 (d, 3 H), 1.55–2.40 (m, 6 H), 2.85–3.90 (m, 8 H), 6.50–6.75 (m, 2 H), 6.85–7.10 (m, 1 H); MS, *m/z* (relative intensity) 261 (18), 232 (100), 161 (94).

***trans*-8-Hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin (9):** GC (240 °C) homogeneous, t_R = 6.1 min; ^1H NMR (CD_3OD) δ 0.97 (t, 6 H), 1.32 (d, 3 H), 1.45–2.05 (m, 5 H), 2.05–3.9 (m, 9 H), 6.55–6.80 (m, 2 H), 6.90–7.15 (m, 1 H); MS, *m/z* (relative intensity) 261 (18), 232 (100), 161 (83).

Pharmacology. Biochemistry. Animals used in the biochemical experiments were male rats of Sprague–Dawley strain (ALAB, Stockholm), weighing 200–300 g. All substances to be tested were dissolved in saline immediately before use, occasionally with a few drops of glacial acetic acid in order to obtain complete dissolution. Reserpine (Ciba-Geigy) was dissolved in a few drops of glacial acetic acid and made up to volume with 5.5% glucose solution. Injection volumes were 5 or 10 mL/kg, and injection solutions had approximately neutral pH.

The biochemical experiments were performed as previously described[8] with a modification; the brain levels of DOPA and 5-HTP were analyzed by use of HPLC with electrochemical detection.[18] Separate dose-response curves based on four to six dose levels for each substance (subcutaneous administration) and brain area were constructed. From these curves, the ED_{50} values and the 95% confidence limits (Table I) were calculated, employing a computerized version of the method of Litchfield and Wilcoxon.[19]

Acknowledgment. We thank Lena Klaesson for skillful synthetic assistance and Ingrid Bergh, Boel Göransson, and Lucia Gaete for skillful assistance in the pharmacological testing. Financial support from Stiftelsen Bengt Lundkvists Minne, Astra Läkemedel AB, The Swedish Board of Technical Development, The Swedish Medical Research Council (Grant No. 155 and 7486), Knut och Alice Wallenberg's Stiftelse, "Krapperups-Stiftelsen",

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Registry No. (±)-**3**, 110270-99-0; (±)-**4**, 110271-02-8; (±)-**4**·HCl, 110271-00-6; (+)-**4**, 110271-03-9; (+)-**4**·HCl, 110271-05-1; (−)-**4**, 110271-04-0; (−)-**4**·HCl, 110271-06-2; (±)-**5**·HCl, 110271-01-7; (±)-**6**·HCl, 110271-07-3; (+)-**6**, 110271-08-4; (+)-**6**·HCl, 110271-10-8; (−)-**6**, 110271-09-5; (−)-**6**·HCl, 110271-11-9; (±)-**7**·HCl, 110271-12-0; (±)-**8**, 110312-33-9; (+)-**8**·HCl, 110351-03-6; (−)-**8**·HCl, 110312-35-1; (±)-**9**, 110312-34-0; 8-methoxy-2-tetralone, 5309-19-3.

Synthesis, Chemical Reactivity, and Antileukemic Activity of 5-Substituted 6,7-Bis(hydroxymethyl)pyrrolo[1,2-*c*]thiazole Biscarbamates and the Corresponding Sulfoxides and Sulfones[1]

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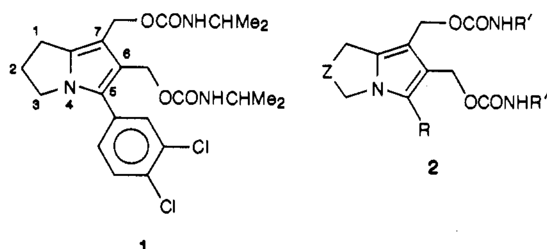
Received May 1, 1987

A series of bis(*N*-methylcarbamate) and bis[*N*-(2-propyl)carbamate] derivatives of 5-substituted 6,7-bis(hydroxymethyl)pyrrolo[1,2-*c*]thiazoles was prepared. The compounds were tested for activity in vivo against P388 lymphocytic leukemia, and the chemical reactivities of the compounds were compared by using the model nucleophile 4-(4-nitrobenzyl)pyridine (NBP). The 5-(3,4-dichlorophenyl)-substituted biscarbamates **6b**, **8b**, and **12b** were inactive and unreactive toward NBP. The 5-methyl-substituted biscarbamates **6a**, **7a**, **8a**, **9a**, **12a**, and **13a** were all active against murine P388 lymphocytic leukemia. The chemical reactivities of the active compounds depended on the oxidation state of the sulfur. The reactivity toward NBP followed the order S > SO >> SO_2. The sulfones **12a** and **13a** are the most active compounds in this series, and their lack of reactivity toward NBP led to the suggestion that **12a** and **13a** are activated in vivo.

The dihydropyrrolizine biscarbamate **1** has been shown to possess significant, reproducible activity against a wide range of experimental murine neoplasias and human tumor xenografts in nude (Nu/Nu) mice.[2] Thus, as part of our continuing interest in this and related systems, we undertook the synthesis and evaluation of a related pyrrolo[1,2-*c*]thiazole series, **2**. These compounds would be



expected to have modified lipophilic and reactive characteristics compared to **1**. The replacement of the C-2 methylene in **1** by sulfur would be expected to reduce the lipophilicity of the compound and successive oxidation at sulfur would reduce the lipophilicity still further. This is apparent when the aromatic-based π values, or the aliphatic fragment values, Fr, are compared (Table I).

For example, the log P[3] (the logarithm of the partition coefficient, P) of **2** would be expected to be reduced by

Table I

substituent	π	Fr
CH_2	0.54	0.54
S	0.05[a]	−0.79[b]
S(O)	−2.14[a]	−3.01[b]
$S(O)_2$	−2.19[a]	

[a] Calculated from the π values[3] for XCH_3 by subtraction of 0.56 (π_{CH_3}). [b] Calculated from the Fr values[3] of XCH_3 by subtraction of 0.77 (Fr_{CH_3}).

2.68–3.55 (depending upon whether π or Fr was used) in the change from Z = CH_2 to Z = S(O).

The pyrrolizine biscarbamate **1** was designed to act as a bifunctional electrophile where the carbamate moieties serve as leading groups in an *O*-alkyl ester cleavage reaction. Thus, electron-withdrawing substituents on the pyrrole ring would be expected to reduce the reactivity of the electrophile through destabilization of an electron-deficient transition state. The C-2 methylene group in **1** is a mild electron donating group (F = −0.04) while the sulfur (F = 0.25), sulfoxide (F = 0.50), and sulfone (F = 0.59) are all electron withdrawing. The sulfur/oxidized sulfur moieties would therefore be expected to reduce the reactivity of **2** (relative to Z = CH_2). Furthermore, the sulfide should be more reactive than either the corresponding sulfoxide or the sulfone. Consequently, the oxidized sulfur compounds could potentially serve as prodrugs for the sulfide, where the requisite reduction could occur in an hypoxic tumor cell.

This prodrug approach offers two potential advantages. First, the prodrug may exhibit some selective toxicity against hypoxic (solid) tumor masses. Second, the prodrug with its potential enhanced stability may be easier to formulate than **1** in a clinical dosage form. The oxidized sulfur compounds may also be dual-function radiation sensitizers. This report describes the preparation and preliminary evaluation of **2** [Z = S, S(O), and $S(O)_2$; R = CH_3 and 3,4-Cl_2Ph; R′ = CH_3 and $CHMe_2$].[4]

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0022-2623/87/1830-2109$01.50/0 © 1987 American Chemical Society